PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 26 January 1999 (26.01.99)	
International application No. PCT/DK98/00245	**Applicant's or agent's file reference** 19465 PC1
International filing date (day/month/year) 11 June 1998 (11.06.98)	**Priority date** (day/month/year) 11 June 1997 (11.06.97)
Applicant THØGERSEN, Hans, Christian et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 January 1999 (08.01.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

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Authorized officer

Lazar Joseph Panakal

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PLOUGMANN, VINGTOFT & PARTNERS A/S
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PLOUGMANN VINGTOFT & PARTNERS
17 SEP. 1999
AML/KHO

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	15.09.99
Applicant's or agent's file reference: 19465 PC1	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK98/00245	11/06/1998	11/06/1997

Applicant
TH GERSEN, Hans, Christian et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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PATENT COOPERATION TREATY

PCT

REC'D 17 SEP 1999
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
19465 PC1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK98/00245	11/06/1998	11/06/1997
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant THØGERSEN, Hans, Christian et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/01/1999	15.09.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Chavanne, F Telephone No. +49 89 2399 8399

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK98/00245

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-72 as originally filed

Claims, No.:

1-54 with telefax of 21/06/1999

Drawings, sheets:

1/21-21/21 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☒ the claims, Nos.: 55
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-54
	No:	Claims	
Inventive step (IS)	Yes:	Claims	9-11, 20
	No:	Claims	1-8, 12-19, 21-54
Industrial applicability (IA)	Yes:	Claims	1-33, 36, 37, 40-45
	No:	Claims	34, 35, 38, 39, 46-54

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The examination of the present application has been performed assuming that the claimed priority is valid. It is noted that intermediate documents would then become relevant to assess the patentability of any claimed subject matter not entitled to said priority.

2. Reference is made to the following document:

   D1: WO 95/31540
   D2: WO 94/18227

3. The prior art does not specifically teach any polypeptide construct comprising a tetranectin trimerising structural element linked to a heterologous moiety. Thus, claims 1-54 appear to be novel.

4. The closest prior art to evaluate the inventiveness of the present application is D1. The problem to be solved by the present application was to provide alternative carrier molecules to be used in e.g. protein library technology, diagnostic and therapeutic systems.
   The solution provided by the present application is a polypeptide construct comprising at least one tetranectin trimerising structural element linked to a heterologous moiety.
   D1 describes trimerising polypeptides linked on their N- and/or C-terminus to a heterologous moiety such as a ligand binding structure, antigens, compounds reactive upon activation, organic compounds, binding domains lipids, DNA or RNA derivatives, enzymes, etc..., which can be used in imaging, diagnostics, gene therapy, genomic library construction, etc... (Page 3, lines 7-22; Page 20 line 14 to page 24 line 18).
   The polypeptides of D1 are derived from the self-assembling structural motif of a C-terminal collagen triple-helical structure, which induces the non-covalent tight association of trimers of Alpha-helices (Page 16, lines 21-25). The polypeptides

sequence show the presence of repeated heptads, wherein the first and fourth amino acid positions in the N- to C-terminal direction correspond mostly to conserved hydrophobic amino acid residues (Page 8 lines 1-8).
D1 also discloses methods for the production of said polypeptides (Page 14, line 15 to page 16, line 12).

The subject-matter of claims 1-3, 7, 8, 12-19, 21-27, 31-33 differs from the teaching of D1 in that the polypeptide linked to the heterologous moiety does not correspond to the trimerising structural element of tetranectin but to the trimerising structural element of collectin, which also forms stable trimers without involving disulfide bridges.

However, D2 shows that the tetranectin region stretching from amino acids 17 to 52 of the mature tetranectin governs the non-covalent linking of the single-chain subunits. D2 also provides the constructs containing said structural element responsible for the multimerisation of the protein (example 9).

Thus, the man skilled in the art, being aware that tetranectin is a trimer (see e.g. description page 2, line 2), would not require any inventive skill to combine the teaching of D1, which describes a construct comprising a trimerising structural element linked to a heterologous moiety, used as a carrier molecule, with D2, which describes a similar trimerising structural element, and come to the subject-matter of claims 1-3, 7, 8, 12-19, 21-27, 31-33. Thus, these claims are not inventive.
It is known in the art, that polypeptides able to form multimers can be covalently linked by a spacer, under the condition that said spacer is sufficiently long and flexible to allow the polypeptides to come into contact. Thus, by further applying common knowledge and commonly used technics, the man skilled in the art would also come to the subject-matter of claims 4-6.
The use of a non inventive product in a kit comprising known devices does not render said kit inventive. Known methods based on a non inventive product and the use of a non inventive product according to known methods are also not inventive. Thus, claims 28-30 and 34-54 are not inventive.
Therefore, claims 1-8, 12-19, 21-54 do not meet the requirements of Article 33(3) PCT.

4. The subject-matter of claims 9-11 refers to the consensus sequence of Tetranectin Trimerising Structural Elements. Such a sequence is neither disclosed nor suggested in the prior art. Thus, the subject-matter of claims 9-11 appears to be inventive.
   The subject-matter of claim 20 differs from the teaching of D1 in that the polypeptide linked to the heterologous moiety, which corresponds to the trimerising structural element of collectin, forms more stable trimers. The trimers of D1 are not stable at 50°C (example 3, D1), whereas the trimers of the present application are stable at even higher temperatures (example 3 and figure 12). This stability at higher temperature is at least a distinguishing feature, but the relevance thereof is not recognisable. Thus, the subject-matter of claim 20 could be considered as inventive (Art. 33(3) PCT).

5. By a clear definition of the Tetranectin Trimerising Structural Element (TTSE) by its structural features (e.g. amino acid sequence), it seems that inventiveness might be acknowledged for the subject-matter of claims 1-54.

VI. Certain documents cited

Certain published documents (Rule 70.10)

1. Protein Science
   Vol. 6, No. 7, pp. 1511-1515, July 1997

2. FEBS Letters
   Vol. 412, No. 2, pp. 388-398, July 1997

VIII. Certain observations on the international application

A problem of the present application is the clear definition of the matter for which protection is sought.

1. Claim 1 lacks clarity in that the expression "tetranectin trimerising structural

element (TTSE)" has no well-recognised meaning, it is an internal designation. Claims 1 and 2 attempt to define said TTSE in terms of the result to be achieved ("being capable of..."). However, this definition is not sufficient to adequately define this compound. A protein being a chemical compound has to be characterised by structural features (e.g. amino acid sequence) (Art. 6 PCT, see also PCT-Guideline, III-4.7a).
Claim 1 is also too vague in that the heterologous moiety is not defined, and as a consequence, the scope of this claim is not clearly defined (Art. 6 PCT).
Moreover, the scope of claims 1 and 31 are limited by a disclaimer. It appears that the use of these disclaimers could be avoided by the clear definition of said heterologous moiety (Art. 6 PCT, see also PCT-Guidelines, III-4.12).
Claim 2 tries to define said heterologous moiety by a negative feature. The corresponding formulation is not clear and thus open to interpretations (Art. 6 PCT).

2. Considering that the present specification teaches polypeptides with only three different kinds of heterologous moiety: a ubiquitin (example 3), antibody fragments (example 4) and a moiety facilitating purification of the polypeptide (example 2), the subject-matter of claim 3 referring to many different heterologous moieties is unduly broad and gives rise to an objection under Article 6-support PCT.

3. The subject-matter of claim 11 is not supported by the description in that it is only based on the speculation that the mentioned amino acid residues may be safely substituted (Page 21, lines 31 and 32). Thus, claim 11 does not meet the requirements of Article 6 PCT.

4. Claims 12 and 13 lack clarity in that the formula a-b-c-d-e-f for the designation of amino acid residues does not have any well-recognised meaning, and thus, is open to interpretation (Art. 6 PCT).

5. Claims 18 and 24 lack clarity in that the expression "to disfavour formation of..." is a definition in terms of the result to be achieved without indicating the means by which this is achieved. Moreover, this term is a relative term which per se is inadmissible under Article 6 PCT.

6. Claim 19 is open to objection under Article 6 PCT in that the formulation does not allow to clearly understand what is claimed (Art. 6 PCT). Moreover, claim 19 seems to refer to two different products, an oligomer comprised of two monomer polypeptide constructs and an oligomer comprised of three monomer polypeptide. Therefore, claim 19 should be reformulated and drafted in two different claims.

7. Moreover, the description does not give any indication for the production of a monomer polypeptide construct comprising a heterologous moiety, wherein said heterologous moiety corresponds to most of the moieties listed in claim 3 (e.g. a toxin, a radioactive moiety, a non-protein-aceous polymer, a polyalcohol, a polysaccharide, a lipid, a polyamine, a photo cross-linking agent). Thus, the information given in the specification is insufficient to enable the skilled man to prepare such monomer polypeptide constructs without the need of intensive experimentation of undue burden (Art. 5 PCT).

8. For the assessment of the present claims 34, 35, 38, 39, 46-54 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

1. A monomer polypeptide construct comprising at least one tetranectin trimerising structural element (TTSE) which is covalently linked to at least one heterologous moiety, said TTSE being capable of forming a stable complex with two other TTSEs, with the proviso that the heterologous moiety is different from any of the fusion proteins CIIH6FXTN123, H6FXTN123, H6FXTN12, H6FXTN23, the sequences of which are shown in SEQ ID NOs: 24-27.

2. A monomer polypeptide construct comprising at least one tetranectin trimerising structural element (TTSE) which is covalently linked to at least one heterologous moiety, said TTSE being capable of forming a stable complex with two other TTSEs, said at least one heterologous moiety being one which does not exclusively facilitate expression and/or purification of the monomer polypeptide construct.

3. A monomer polypeptide construct according to claim 1 or 2, wherein the stable complex includes a triple alpha helical coiled coil.

4. A monomer polypeptide construct according to any of the preceding claims, wherein the heterologous moiety is selected from the group consisting of a ligand binding structure; a toxin; a detectable label; an *in situ* activatable substance; an enzyme; a radioactive moiety; a cytokine; a non-proteinaceous polymer such as a polymeric alkaloid, a polyalcohol, a polysaccharide, a lipid and a polyamine; a photo cross-linking agent; and a group facilitating conjugation of the monomer polypeptide construct to a target.

5. A monomer polypeptide construct according to any of the preceding claims, which comprises 2 TTSEs which are covalently linked by a spacer moiety which allows both of the 2 TTSEs to take part in complex formation with a third TTSE not being part of the monomer polypeptide construct.

Replaced by Article 34

6. A monomer polypeptide construct according to claim 5, wherein the spacer moiety has a length and a conformation which favours complex formation involving both of the two TTSEs which are covalently linked by the spacer moiety.

7. A monomer polypeptide construct according to claim 5 or 6, wherein the spacer moiety is a polypeptide fragment.

8. A monomer polypeptide construct according to any of claims 1-4, which comprises one single TTSE.

9. A monomer polypeptide construct according to any of the preceding claims, wherein the TTSE is derived from human tetranectin, murine tetranectin, C-type lectin of bovine cartilage, or C-type lectin of shark cartilage.

10. A monomer polypeptide construct according to claim 9, wherein the TTSE comprises a polypeptide sequence which has at least 68% sequence identity with the consensus sequence shown in Fig. 2.

11. A monomer polypeptide construct according to claim 10, wherein the sequence identity with the consensus sequence is at least 75%, such as at least 81%, at least 87%, or at least 92%.

12. A monomer polypeptide construct according to any of claims 9-11, wherein at least one amino acid residue selected from the group consisting of amino acid residue nos. 6, 21, 22, 24, 25, 27, 28, 31, 32, 35, 39, 41, 42, is/are substituted by any non-helix breaking amino acid residue, the amino acid residue numbering referring to amino acid residues in SEQ ID NO: 7.

13. A monomer polypeptide construct according to any of the preceding claims, wherein the at least one TTSE comprises a repeated heptad having the formula a-b-c-d-e-f-g (N to C),

wherein a majority of the amino acids residues a and d are hydrophobic amino acids.

14. A monomer polypeptide construct according to claim 13, wherein heptad is repeated 3 times and wherein the last occurrence of the heptad has a glutamine residue corresponding to residues a and d.

15. A monomer polypeptide construct according to any of the preceding claims, wherein the at least one heterologous moiety is covalently linked to the TTSE via a peptide bond to the N- or C-terminus of the TTSE peptide chain, via a peptide bond to a side chain in the TTSE, via a bond to a cysteine residue, or when more than one heterologous moity, combinations of these locations.

16. A monomer polypeptide construct according to any of the preceding claims which lacks any free amino and/or carboxy groups.

17. A monomer polypeptide construct according to any of the preceding claims which lacks a substantial part of the N-terminal region of tetranectin which is encoded by exon 1.

18. A monomer polypeptide construct according to any of the preceding claims comprising two heterologous moieties which are linked via peptide bonds to the N- and C-terminus, respectively.

19. A monomer polypeptide construct according to any of the preceding claims which is constructed so as to disfavour formation of complexes between identical TTSEs.

20. An oligomer which is comprised of two monomer polypeptide constructs according to any of claims 1-19, and which comprises at three TTSE's or a multiplum of three TTSE's, or which is comprised of three monomer polypeptide constructs according to any of claims 1-4 or 8-19.

21. An oligomer according to claim 20 which is stable in the temperature range 50-70°C.

22. An oligomer according to claim 20 or 21, which comprises at least one heterologous moiety which is positioned N-terminally to a TTSE and at least one heterologous moiety which is positioned C-terminally to a TTSE.

23. An oligomer according to claim 22, wherein the at least one heterologous moiety which is positioned N-terminally to a TTSE and the at least one heterologous moiety which is positioned C-terminally to a TTSE are part of the same monomeric polypeptide construct.

24. An oligomer according to claim 22, wherein the at least one heterologous moiety which is positioned N-terminally to a TTSE and the at least one heterologous moiety which is positioned C-terminally to a TTSE are part of two separate monomeric polypeptide constructs.

25. An oligomer according to any of claims 20-24, wherein each monomer polypeptide construct is designed so as to disfavour formation of trimers including two monomer polypeptide constructs having identical TTSEs.

26. A method of preparing a monomer polypeptide construct according to any of claims 1-19, the method comprising

- isolating the monomer polypeptide construct from a culture comprising a host cell which carries and expresses a nucleic acid fragment which encodes the monomer polypeptide construct, or

- synthesizing, by means of chemical peptide synthesis, the monomer polypeptide construct and subsequently isolating the monomer polypeptide construct from the reaction mixture, or

- preparing a TTSE in a culture comprising a host cell which carries and expresses a nucleic acid fragment which encodes the TTSE, subsequently linking covalently at least one heterologous moiety to the TTSE, and thereafter isolating the resulting monomer polypeptide construct, or

- synthesizing, by means of chemical peptide synthesis, a TTSE, subsequently linking covalently at least one heterologous moiety to the TTSE, and thereafter the isolating the resulting monomer polypeptide construct from the reaction mixture,

and optionally subjecting the monomer polypeptide construct to further processing.

27. A method for preparing a dimeric oligomer according to claim 20 which comprises

- admixing a monomer polypeptide construct according to any of claims 1-19 which includes two TTSEs (construct 1) with a monomer polypeptide construct according to any of claims 1-4 or 8-19 which includes only one TTSE (construct 2),

- effecting the two TTSE's of construct 1 to complex with the TTSE of construct 2, and

- isolating the resulting dimer and optionally subjecting the dimer to further processing.

28. A method for preparing a trimeric oligomer according to claim 20 which comprises

- admixing three monomer polypeptide constructs according to any of claims 1-19 with each other,

- effecting complex formation between one TTSE of each monomer polypeptide construct, and

- isolating the resulting trimer and optionally subjecting the trimeric oligomer to further processing.

29. A kit comprising

- a first package comprising at least one container means, each at least one container means containing a monomer polypeptide construct according to any of claims 1-19,

- a second package comprising at least one container means, each at least one container means in the second package containing a monomer polypeptide construct according to any of claims 1-19, the second package being different from the first package with respect to choice and/or number of monomer polypeptide constructs included therein, and optionally

- a third package comprising at least one container means, each at least one container means in the third package containing a monomer polypeptide construct according to any of claims 1-19, the second package being different from the first and second packages with respect to choice and/or number of monomer polypeptide constructs included therein.

30. A kit according to claim 29, wherein the at least one container means in each package contains mutually distinct monomer polypeptide constructs.

31. A kit according to claim 29 or 30, wherein all container means comprised in the kit comprises mutually distinct polypeptide constructs.

32. A nucleic acid fragment in isolated form which encodes a TTSE as defined in any of claims 1-19 or which encodes the polypeptide part of a monomer polypeptide construct according to any of claims 1-19, with the proviso that the nucleic acid fragment is different from one that encodes native members of

the tetranectin family, and that the nucleic acid fragment is different from one that encodes any of the fusion proteins CIIH6FXTN123, H6FXTN123, H6FXTN12, H6FXTN23, the sequences of which are shown in SEQ ID NOs: 24-27.

33. A replicable vector which comprises a nucleic acid fragment according to claim 32.

34. A transformed host cell, which comprises a nucleic acid fragment according to claim 32 or a replicable vector according to claim 32.

35. Use of a monomer polypeptide construct according to any of claims 1-19 or to a an oligomer construct according to any of claims 20-25 for targeted gene therapy involving selective delivery of the material for transfection or infection of the specific population of cells.

36. The use according to claim 35 wherein the at least one heterologous moity comprises a moiety selected from a ligand binding structure such as a receptor molecule or the ligand binding part of a receptor molecule, and wherein the gene therapy involves the delivery of nucleic acids to the desired population of cells by use of a viral vector directed to cells displaying the artificial receptor complex corresponding to the heterologous moity.

37. The use of a monomer polypeptide construct according to any of claims 1-19 or to a an oligomer according to any of claims 20-25 as a component of a chimaeric product having low antigenicity in humans relative to formulations comprising on or more components of non-human origin.

38. The use of a monomer polypeptide construct according to any of claims 1-19 or to a an oligomer according to any of claims 20-25 as a vehicle for assembling antibody fragments into oligomeric or multivalent entities for generating

chimeric artificial antibodies having preselected pharmacokinetic and/or pharmadynamic properties.

39. The use of a monomer polypeptide construct according to any of claims 1-19 or to a an oligomer according to any of claims 20-25 for delivering an imaging or toxin-conjugated antibody to a tumor.

40. The use of a monomer polypeptide construct according to any of claims 1-19 or to a oligomer according to any of claims 20-25 as a vehicle delivering an substance to a target cell or tissue.

41. The use of a monomer polypeptide construct according to any of claims 1-19 or to a oligomer according to any of claims 20-25 for a labelled construct wherein the label is coupled to one or to of the TTSE monomer units.

42. The use of a monomer polypeptide construct according to any of claims 1-19 or to a oligomer according to any of claims 20-25 for protein library technology, such as phage display technology.

43. The use according to claim 42 comprising a poly nucleotide molecule encoding one or more TTSE.

44. The use according to claim 43 comprising a vector encoding one or more TTSE.

45. The use of a monomer polypeptide construct according to any of claims 1-19 or to a oligomer according to any of claims 20-25 for the preparation of a pharmacutical composition.

46. The use according to any to claim 45, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

47. The use according to claim 45 or 46 wherein the pharmaceutical composition is administered by a route selected from the group consisting of the intraveneous route, the intraarterial route, the transmembraneus route of the buccal, anal, vaginal or conjunctival tissue, the intranasal route, the pulmonary route, the transdermal route, the intramuscular routed, subcutaneous route, intratechal route, inoculation into tissue such as a tumour, or by an implant.

48. The use according to any of claims 35 to 47 wherein the monomer polypeptide construct according to any of claims 1-19 or the oligomer according to any of claims 20-25 is comprised in a liposome

49. A method for treating or preventing of a disease comprising administering to the subject in need thereof an effective amount of a pharmceutical composition as defined in any of claims 45 and 46.

50. A method for treating or preventing a disease comprising administering to the subject in need thereof an effective amount of a relevant pharmceutical coupled to a monomer polypeptide construct according to any of claims 1-19 or to a oligomer according to any of claims 20-25.

51. A method for targeted gene therapy comprising use of a monomer polypeptide construct according to any of claims 1-19 or to a oligomer according to any of claims 20-25.

52. A method of human gene therapy comprising use of a monomer polypeptide construct according to any of claims 1-19 or to an oligomer according to any of claims 20-25 wherein at least one TTSE is modifyed with a membrane integrating or associating entity having affinity to the specific population of cells in the body relevant for the gene therapy.

53. A method according to any of claims 49 to 52

wherein the monomer polypeptide construct according to any of claims 1-19 or the oligomer according to any of claims 20-25 is administered by a route selected from the group consisting of the intraveneous route, the intraarterial route, the transmembraneus route of the buccal, anal og vaginal tissue, intranasal route, the pulmonary route, the transdermal route, intramuscular, subcutaneous, intratechal, the buccal, inoculation into tissue such as a tumour, or by an implant.

54. A method for prevention and/or treating a disease, comprising administering to a mammal in need thereof a prophylactically or therapeutically effective amount of a construct comprising the monomer polypeptide construct according to any of claims 1-19 or the oligomer according to any of claims 20-25.

55. A method for diagnosis comprising a construct comprising the monomer polypeptide construct according to any of claims 1-19 or the oligomer according to any of claims 20-25 together with a diagnosing component coupled thereon.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
19465 PC1		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/DK 98/ 00245	11/06/1998	11/06/1997
Applicant		
THØGERSEN, Hans, Christian et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 1
   - [ ] as suggested by the applicant.
   - [X] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00245

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see further information sheet

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 35, 36, 39, 47-54 and claim 40 as far as in vivo methods are concerned are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claim 55 as far as in vivo methods are concerned is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 98/00245

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N15/62 C12N1/21 C07K14/47 C07K16/00
C07K19/00 A61K31/70 A61K48/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 18227 A (DENZYME APS ;THOGERSEN HANS CHRISTIAN (DK); HOLTET THOR LAS (DK);) 18 August 1994 cited in the application see page 52, line 1 - line 14; figures 20,21; example 9 ---	1-55
A	L. BERGLUND AND T.E. PETERSEN: "The gene structure of tetranectin, a plasminogen binding protein" FEBS LETTERS, vol. 309, no. 1, 1992, pages 15-19, XP002077572 ELSEVIER, AMSTERDAM, NL cited in the application see the whole document --- -/--	1-55

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 1998	01/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hornig, H

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 206 400 A (TNO) 30 December 1986 see the whole document	1-55
A	WO 95 31540 A (MEDICAL RES COUNCIL ;HOPPE HANS JUERGEN (GB); REID KENNETH BANNERM) 23 November 1995 cited in the application see the whole document	1-55
A	WO 96 37621 A (MORPHOSYS PROTEINOPTIMIERUNG ;PACK PETER (DE); HOESS ADOLF (DE)) 28 November 1996 see the whole document	1-55
A	OSBOURN J K ET AL: "GENERATION OF A PANEL OF RELATED HUMAN SCFV ANTIBODIES WITH HIGH AFFINITIES FOR HUMAN CEA" IMMUNOTECHNOLOGY, vol. 2, no. 3, September 1996, pages 181-196, XP000645453 see the whole document	1-55
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 98/00245

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WO 9637621 A	28-11-1996	EP 0827544 A	11-03-1998

CORRECTED VERSION*

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, 15/62, 1/21, C07K 14/47, 16/00, 19/00, A61K 31/70, 48/00

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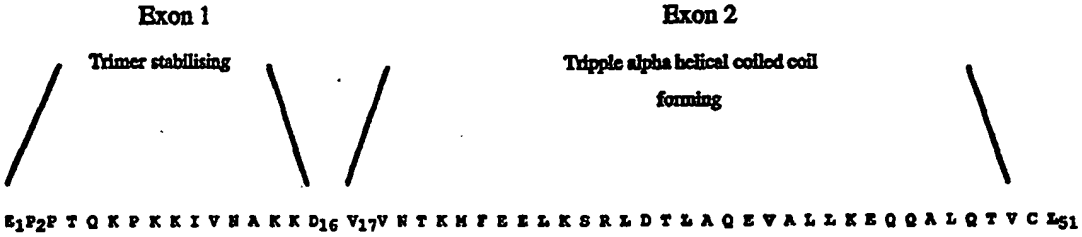
Published
With international search report.

(54) Title: TRIMERISING MODULE



(57) Abstract

The present invention relates to the design of trimeric polypeptides using polypeptide structural elements derived from the tetranectin protein family, and their use in rational *de novo* design and production of multi–functional molecules including the application of the multi–functional molecules in protein library technology, such as phage display technology, diagnostic and therapeutic systems, such as human gene therapy and imaging. The trimeric polypeptides being constructed as a monomer polypeptide construct comprising at least one tetranectin trimerising structural element (TTSE) which is covalently linked to at least one heterologous moiety, said TTSE being capable of forming a stable complex with two other TTSEs; or as an oligomer which is comprised of two monomer polypeptide constructs as mentioned above, and which comproses three TTSEs or a multiplum of three TTSEs, or which is comprised of three monomer polypeptide constructs.

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